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Review

The role of glucocorticoid receptors in metabolic syndrome and psychiatric illness

Andreas G. Moraitis[a,*], Thaddeus Block[a,b], Dat Nguyen[a], Joseph K. Belanoff[a,b,*]

[a] Corcept Therapeutics, 149 Commonwealth, Menlo Park, CA, United States
[b] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, United States

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ABSTRACT

Glucocorticoids (GCs) are involved in a large number of the physiological changes associated with metabolic syndrome and certain psychiatric illness. Although significance is often given to the concentration of GC, its biological action is determined by the activation of intracellular GC receptors (GR). Genetic polymorphisms of the GR and the large array of GR related cofactors can directly or indirectly affect the pathophysiology and evolution of these conditions. This review will discuss the effects of GR mutations on metabolic syndrome and psychotic depression.

Contents

1. Introduction

Glucocorticoids (GCs) play an integral role in a wide array of physiological systems in the body, affecting lipid and glucose metabolism, immunosuppressive and anti-inflammatory reactions, growth, reproduction and brain function. The effects of cortisol are largely mediated by the GC receptor (GR). In its unbound form, GR resides in the cytoplasm as part of a large multiprotein complex comprising of chaperones (hsp90, hsp70), co-chaperones, and immunophilins (FK506-binding protein) (Fig. 1) [1]. Upon binding with cortisol, conformational changes occur, leading to the dissociation of GR from the multiprotein complex. GR-GR dimers are often formed. The activated, ligand bound GR complex then translocate to the nucleus, where it functions as a transcription factor to regulate gene expression by binding at specific glucocorticoid response elements regulating both transactivation or transrepression. The mechanism of transactivation of gene expression usually involves GR dimers, binding with specific glucocorticoid response elements and activating gene expression. The transrepression mechanism involves the activated GR interacting with transcription factors, like AP-1 and NF-κB, preventing them from binding to their target genes. This interaction can sometime allow GR to indirectly regulate gene expression The transrepression mechanism involves the activated GR interacting with transcription factors, like AP-1 and NF-κB, preventing them from binding to their target genes. This interaction can sometime allow GR to regulate gene expression indirectly in the absence of direct DNA binding [2,3].

* Corresponding author.
E-mail address: Amoraitis@corcept.com (A.G. Moraitis).

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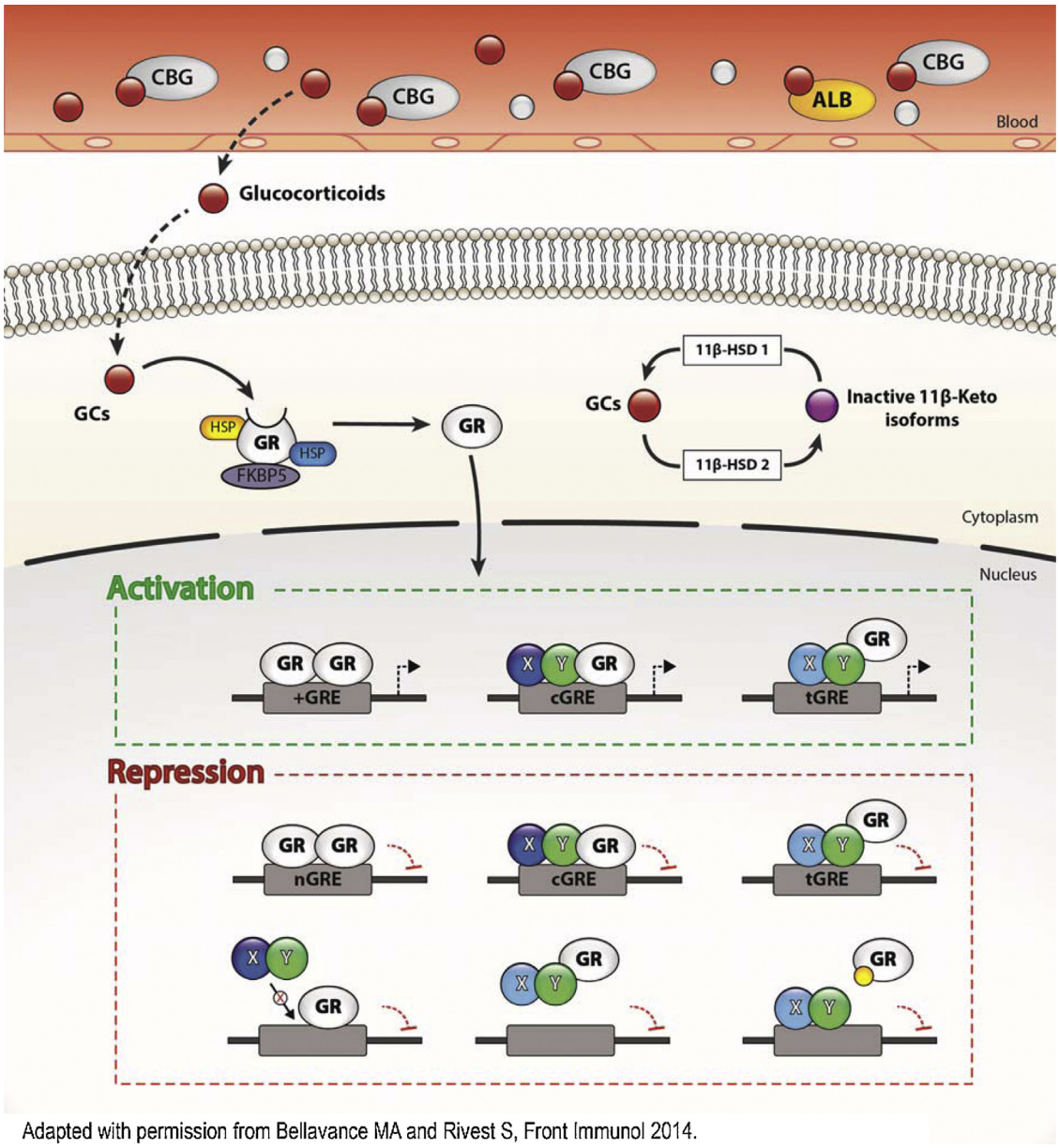

Fig. 1. Glucocorticoid Receptors' Role in the Regulation of Gene Transcription: Unbound glucocorticoids (GCs) diffuse through the cell membranes binding to GC receptors (GR) residing in the cytoplasm as part of a large multiprotein complex comprising of chaperones (hsp90, hsp70) and immunophilins (FKBP5). The bioavailability of endogenous GCs at the cellular level is limited by enzymatic metabolism (11β-HSD enzymes). The activated GR then translocates to the nucleus to modulate the gene transcription process. Liganded GRs bind to four main types of GR-response elements (GREs): simple (+GRE), negative (nGRE), composite GREs (cGRE), and interactions (tGRE). The regulation of both transactivation and transrepression is dictated by the type of GRE and its binding partners.

2. Glucocorticoid receptor gene

The human GR gene (NR3C1) is located on chromosome 5 and consists of 9 exons (Fig. 2). Variations in the transcription and translation of the GR gene can lead to seemingly random actions of cortisol. However, these variations are necessary to allows cells and tissues to appropriately adapt to wide concentrations of GC. As an example, alternative splicing of the GR precursor mRNA can give rise to 5 GR protein subtypes- GRα,GRβ, GRγ, GR-A and GR-P. Eight more receptor proteins are produced by alternative translation initiation from GR mRNA [4,5]. The classic GRα isoform can increase GC sensitivity while the GRβ is transcriptionally inactive and is responsible for GC resistance. In addition to the GR isoforms generated by alternative initiation of translation or alternative splicing, four novel receptor variants (GR NS-1, GR DL-1, GR-S1 and GR-S1 (−349A)) [6,7] with multiple amino acid replacements/truncation and unknown functional role have also been discovered. These generic variations may account for the diversity in patient presentations and responses to GC.

2.1. The role of GR expression, degradation and trafficking on glucocorticoid cellular responsiveness

The ability of GC to provoke cellular response is dependent on the GR expression, degradation, and translocation into the nucleus.

The intracellular concentration of GR varies greatly between different cells and tissues and involves a complex combination of regulatory feedback mechanisms at both the transcriptional and